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Synthesis, Structural Analysis, and Reactivity of Bridged Orthoamides by Intramolecular Schmidt Reaction

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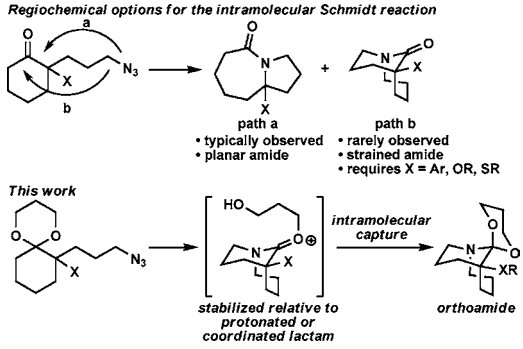
The intramolecular Schmidt reaction is a useful method for the synthesis of lactams.[1] Most commonly, this reaction affords fused lactams bearing a nitrogen atom at a ring fusion position by preferential migration of the carbon bearing the azide-containing side chain. We have recently shown that certain substitution types lead to the alternative regioisomeric product containing a bridged ring system incorporating nitrogen at a bridgehead position (Scheme 1).[2] Such compounds are noteworthy since they contain distorted amide bond linkages, which are of interest from theoretical, mechanistic, and reactivity perspectives.[3] However, these methods are substrate dependent and provide mixtures of bridged and fused lactams, even in the most favorable cases. We now show that intramolecular Schmidt reactions can be reliably steered toward bridged heterocycles containing orthoamides in high yields. The method is broad in scope and allows for systematic study of compounds that are analogous to elusive tetrahedral intermediates of amide addition reactions.[4]

Scheme 1



We hypothesized (1) that the formation of bridged lactams using the Schmidt reaction of ketones and azides was hampered by the necessity of forming a strained nonplanar amide, (2) that this could be mitigated by relying instead on formation of a relatively stable iminium ether intermediate, and (3) that intramolecular capture would provide an easy road to a stable, and unusual, orthoamide product. That we had previously demonstrated that ketals also participate in azido-Schmidt chemistry[5a] combined with a single report of a bridged ring system formed in this way[5b] suggested that reactions of these species might favor bridged products to a greater degree.

To maximize the chance for success, we focused first on alkyl azides that had already been shown to react preferentially by path b (Scheme 1).[2] Thus, Lewis or protic acid treatment of a series of ketals derived from 1,3-dioxolane afforded bridged orthoamides in excellent yield (Table 1). The products were stable to the reaction and chromatographic isolation conditions. As hypothesized, the transformation proceeded with efficient control of regiochemistry, while the ketones corresponding to **1a**−**f** provided a ca. 5:2 mixture of bridged and fused lactams.[2a] These results demonstrate that this approach accommodates a variety of ketal types. In contrast, the behavior of enol ether **1f** shows that success depends upon intramolecular capture of the intermediate oxonium ion and that the [4.3.1] ring system containing a hemiaminal is unstable.

Table 1. Formation of Bridged Orthoamides from Ketals

entry	azide	product	conditions[a]	yield (%)[b]
1	(**1a**) R, R = H	(**2a**)	A	88
2	(**1b**) R, R = -$(CH_2)_4$-	(**2b**)	A	71
3	(**1c**) n = 1, R, R = H	(**2c**)	B	77
4	(**1d**) n = 1, R, R = Me	(**2d**)	B	75
5	(**1e**) n = 2, R, R = H	(**2e**)	B	70[c]
6	(**1f**)	(**2f**)	C	63

[a] (A) $BF_3 \cdot CH_3CN$, 5.0 equiv, 0 °C to rt; (B) $BF_3 \cdot CH_3CN$, 3.0 equiv, −78 °C to rt; (C) TfOH, 5.0 equiv, 0 °C. [b] Isolated after chromatography. [c] Determined by ^1H NMR, see Supporting Information (SI) for details.

Subsequent work showed that a range of conformationally locked azido alkyl 1,3-dioxolanes substituted with aromatic rings in the 2-position could easily be transformed into analogous products (Table 2, entries 1−4). Throughout, these reactions proceeded with complete control of regiochemistry.[6] Even the conformationally flexible azide **1k** (entry 5) gave exclusively a bridged product, in sharp contrast to the corresponding ketone, which *only* afforded fused lactam. A number of substrates with heteroatoms in the 2-position underwent the reaction in good to excellent yields (entries 6−8). Finally, a conformationally flexible azide with a shorter azide chain cleanly furnished the [4.2.1] bridged scaffold (entry 9). It is likely that in this case the fused product did not form due to strain developing en route to the corresponding four-membered lactam containing the fused product.

We have proposed that chairlike cyclohexanones afford bridged products only when the azide-containing side chain and the diazonium cation are both pseudoaxial (Scheme 2, intermediate **C**).[5c] Here, the N_2^+ leaving group is axial, leading to migration of the antiperiplanar alkyl group. We propose that the enhanced regioselectivity observed with ketal-containing vs ketone-containing azides results from steric and electronic repulsion between the diazonium cation in the **D**

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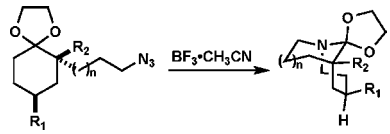
conformation relative to **C**. In both cases, the most stable conformation of the O-alkyl side chain is likely to be as drawn; the N_2^+ leaving group in **D** experiences a disfavorable syn-1,5 interaction with the O-alkyl group that is absent in **C**. In the analogous reactions of ketones, where the OR group is replaced by either a proton or a Lewis acid, such effects are minimized relative to the present case (and the role of attractive nonbonded stabilization between N_2^+ and R_2 is even more important). Interestingly, the Deslongchamps principle of maximal overlap could also come into play here.[4b] Thus, if the side chain orientation proposed predominates in the transition state leading to product, it is only possible for an oxygen electron lone pair to be antiperiplanar to the migrating bond in **C** but not in **D** (where the O-alkyl group is instead antiperiplanar to the darkened bond in **D**). Finally, the success of cases lacking an alkyl group at R indicates that the reactive conformation in these examples is exclusively **B** and not **A**.

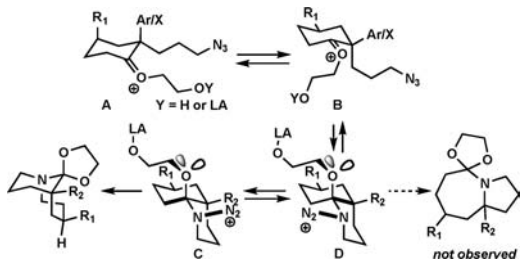
Table 2. Azide Scope[a]



entry	azide	R_1	R_2	*n*	ketal	yield (%)
1	(**1g**)	*t*-Bu	4-(OMe)C_6H_4	1	(**2g**)	92
2	(**1h**)	*t*-Bu	3,4,5-(OMe)$_3C_6H_2$	1	(**2h**)	86
3	(**1i**)	*t*-Bu	3,5-(OMe)$_2C_6H_3$	1	(**2i**)	86
4	(**1j**)	*t*-Bu	4-(NO_2)C_6H_4	1	(**2j**)	94
5	(**1k**)	H	C_6H_5	1	(**2k**)	59
6	(**1l**)	H	OMe	1	(**2l**)	52[b]
7	(**1m**)	H	SMe	1	(**2m**)	50
8	(**1n**)	H	SPh	1	(**2n**)[7]	78[b]
9	(**1o**)	H	C_6H_5	0	(**2o**)	91

[a] BF_3•CH_3CN, 3.0−5.0 equiv in CH_2Cl_2. [b] TMSOTf.

Scheme 2



The α-amino ketal functionality is stabilized by a nonplanar arrangement of atoms. The X-ray crystal structure of **2n** reveals that the N1−C1 bond (1.448 Å) as well as the C1−O1 (1.405 Å) and C1−O2 (1.416 Å) bonds are shorter than typical N−C_{sp3} (1.469 Å) and C_{sp3}−O (1.432 Å) bonds (Figure 1).[4a] The C1−C2 bond length of 1.543 Å is slightly longer than the average C_{sp3}−C_{sp3} bond (1.530 Å).[4a] The torsion angles between N_{lp} and C1−O1 of 69.5° and between N_{lp} and C1−O2 of 46.1° are consistent with the absence of $N_{lp}\rightarrow\sigma^*_{C-O}$ interactions in this system. By contrast, there exists a reasonably good arrangement between $O1_{lp}$ and the N1−C1 bond (∼148°) and between $O2_{lp}$ and the N1−C1 bond (∼158°). While the lengths of C1−O1, C1−O2, and C1−C2 bonds are in agreement with an anomeric effect resulting from $O_{lp}\rightarrow\sigma^*_{C1-N1}$ and $O_{lp}\rightarrow\sigma^*_{C1-C2}$ interactions, the shortened N1−C1 bond seems to be characteristic to the tetrahedral intermediate stabilized by scaffolding effects of a medium-sized ring.[4]

We have begun to examine the reactivity of these α-amino ketals (Scheme 3). For example, we found that acid hydrolysis affords 9-membered ring amino esters (these can be converted into the bridged lactams by treatment with base; see SI). In contrast, chromatography-stable hemiaminal ethers are formed following reduction (DIBAL-H), while reaction with Me_3Al delivers a "twisted enamine". As expected, α-amino ketals also undergo reactions at nitrogen.

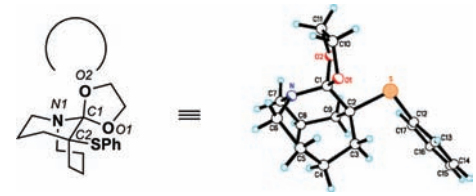
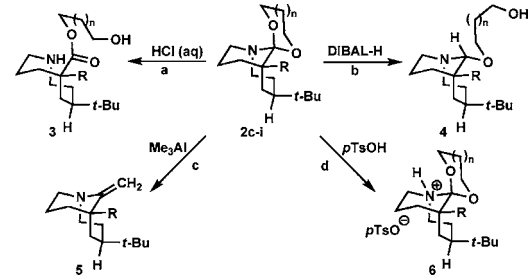


Figure 1. X-ray structure of **2n**. Selected bond lengths [Å] and angles [deg]: N1−C1 1.448, C1−O1 1.405, C1−O2 1.416, C1−C2 1.543, C6−N1−C1−O1 −38.1, C7−N1−C1−O1 177.0, C7−N1−C1−O2 61.5, C6−N2−C1−O1 −153.7.

Scheme 3[a]



[a] Conditions: (a) **2i**, THF, 60 °C, 12 h, 89%. (b) **2c**, PhH, 80 °C, 15 h, 67%. (c) **2d**, CH_2Cl_2, 40 °C, 15 h, 56%. (d) **2h**, rt, 20 h, 96%.

In summary, we have established a direct synthesis of orthoamides, which are analogues of tetrahedral intermediates derived from amide addition reactions. Continuing efforts to study this class of compounds are underway.

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Supporting Information Available: Experimental details characterization data for new compounds, and the .cif file for **2n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Only bridged orthoamides were observed in the analysis of the crude reaction mixtures by ^{1}H NMR. See SI for details.
(7) Lactam **2n** was originally reported in ref 5a as a fused isomer. We now reassign **2n** as a bridged orthoamide. See SI for details.

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